ATENT COOPERATION TRATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

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To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202

ETATS-UNIS D'AMERIQUE in its capacity as elected Office

Date of mailing (day/month/year)
07 November 2000 (07.11.00)

International application No. PCT/CA00/00289

International filing date (day/month/year) 16 March 2000 (16.03.00) Applicant's or agent's file reference 1038-1025

Priority date (day/month/year) 16 March 1999 (16.03.99)

Applicant

LOOSMORE, Sheena, M. et al

1.	The designated Office is hereby notified of its election made: X in the demand filed with the International Preliminary Examining Authority on:	
	11 October 2000 (11.10.00)	
	in a notice effecting later election filed with the International Bureau on:	
2.	The election X was	
	was not	
	made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).	

1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35

The International Bureau of WIPO 34, chemin des Colombettes

Authorized officer

Nestor Santesso

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION THAT INTERNATIONAL APPLICATION CONSIDERED TO BE WITHDRAWN

(PCT Article 14(1), (3) or (4) and Rule 29.1)

From the INTERNATIONAL BUREAU

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as designated Office

Date of mailing (day/month/year) 28 August 2001 (28.08.01)	IMPORTANT NOTIFICATION
International application No. PCT/CA00/00289	International filing date (day/month/year) 16 March 2000 (16.03.00)
Applicant	
CONNAUGHT LABORATORIES LIMITED et al	

1.	The International Bureau hereby gives notice that the receiving Office has, on the date indicated below, notified to the
	applicant that the international application is to be considered withdrawn:

01 June 2001 (01.06.01)

A copy of this notification has been sent to the International Preliminary Examining Authority.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Authorized officer

V. Gross (Fax 338.87.40)

Telephone No.: (41-22) 338.83.38

Facsimile No.: (41-22) 740.14.35 Form PCT/IB/325 (February 1994) PATENT COOPERATION PEATY REC'D 19 JUL 2001
PCT





INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's	or ag	gent's file reference				
1038-10	25		FOR FURTHER A	CTION	Preliminary	ation of Transmittal of International Examination Report (Form PCT/IPEA/416)
Internation	al app	olication No.	International filing date	(day/montl	h/year)	Priority date (day/month/year)
PCT/CA	00/0	0289	16/03/2000			16/03/1999
Internation C07K14		ent Classification (IPC) or nat	iional classification and If	PC .		
Applicant						
CONNA	UGH	T LABORATORIES LIN	/ITED et al			
1. This and is	interr s trar	national preliminary examinational preliminary examinations and the applicant and th	nation report has beer ccording to Article 36.	n prepared	d by this Inter	rnational Preliminary Examining Authorit
2. This	REPO	ORT consists of a total of	9 sheets, including th	is cover sl	heet.	
b (:	een a see F	eport is also accompanied amended and are the basi Rule 70.16 and Section 60 exes consist of a total of 8	is for this report and/o 7 of the Administrative	r sheets c	ontaining rec	n, claims and/or drawings which have stifications made before this Authority e PCT).
3. This r	eport ⊠	contains indications relati	ing to the following ite	ms:		
11		Priority				
111		Non-establishment of op		ovelty, inv	entive step a	nd industrial applicability
IV		Lack of unity of inventior				
V	⋈	Reasoned statement und citations and explanation	der Article 35(2) with r ns suporting such state	egard to n ement	novelty, inven	ntive step or industrial applicability;
VI		Certain documents cited	1			
VII '		Certain defects in the inte	ernational application			
VIII	×	Certain observations on	the international appli	cation		
Date of sub	nissio	n of the demand		Date of co	ompletion of th	is report
11/10/200	00			17.07.20	·	
		address of the international ning authority:	-	Authorize	d officer	SASONES MAZIN
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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00289

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I.	Basis of the report			at at a sta which	have been furnished to
1.		ments of the international ap response to an invitation un to this report since they do n			
	1-13,16,17, 19-63	as originally filed			
	14,15,18	as received on	22/06/2001	with letter of	22/06/2001
	Claims, No.:				
	1-29	as received on	22/06/2001	with letter of	22/06/2001
	Drawings, sheets:				
	1/83-83/83	as originally filed			
	Sequence listing pa	art of the description, page	s:	•	
	2-75, filed with the lef	tter of 29.05.00			
2		nguage, all the elements ma e international application w	arked above were a as filed, unless oth	available or furnishe erwise indicated un	d to this Authority in the der this item.
	These elements were	e available or furnished to th	is Authority in the	following language:	, which is:
	☐ the language of	a translation furnished for th	ne purposes of the	international search	(under Rule 23.1(b)).
	□ the language of	publication of the internation	nal application (und	der Rule 48.3(b)).	·
	☐ the language of 55.2 and/or 55.3	a translation furnished for th 3).	ne purposes of inte	rnational preliminar	
;	 With regard to any n international prelimin 	nucleotide and/or amino ac nary examination was carrie	id sequence discled out on the basis	osed in the internati of the sequence listi	onal application, the ing:
	☐ contained in the	e international application in	written form.		
	☐ filed together w	ith the international applicati	on in computer rea	dable form.	
		equently to this Authority in v	vritten form.		
	M furnished subse	equently to this Authority in (computer readable	form.	
		that the subsequently furnish	hed written sequer en furnished.	nce listing does not (
	☐ The statement	that the information recorde	d in computer read	able form is identica	al to the written sequence

listing has been furnished.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00289

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4	ı. Th	ne a	mendments have re	esulted in the cancellation of:
			ne description,	pages:
			he claims,	Nos.:
	L -		he drawings,	sheets:
	L_	. u	ne diamingo,	and and had not been made, since they have been
	5. D	3 7	This report has bee considered to go be	n established as if (some of) the amendments had not been made, since they have been eyond the disclosure as filed (Rule 70.2(c)):
		((Any replacement s report.)	heet containing such amendments must be referred to under nomination of the second sec
		;	see separate shee	ıt en
	6. <i>F</i>	Addi	tional observations	, if necessary:
	IV 1	l ac	k of unity of inven	tion
	1 1	ln re	sponse to the invite	ation to restrict or pay additional fees the applicant has:
			restricted the clain	
		Ø	paid additional fee	
			paid additional fee	es under protest.
			neither restricted	nor paid additional fees.
			co t not to invite	and that the requirement of unity of invention is not complied and chose, according to Rule the applicant to restrict or pay additional fees.
	3.	Thi	is Authority conside	ers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
)			complied with.	
		Ø	- coo congrate sh	n for the following reasons:
	4	. Co	onsequently, the folk camination in estab	llowing parts of the international application were the subject of international preliminary lishing this report:
		×	all parts.	
			the parts relating	g to claims Nos
	`	/. R c		nt under Article 35(2) with regard to novelty, inventive step or industrial applicability; mations supporting such statement
			Statement	

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/CA00/00289

Novelty (N)

Yes:

Claims 1-2,4-29

No:

Claims 3

Inventive step (IS)

Claims 4 Yes:

No:

Claims 1-3,5-29

Industrial applicability (IA)

Claims 1-29 Yes: Claims

No:

2. Citations and explanations see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

INTERNATIONAL PRELIMINARY Inte

D1: WO 96 30519 A (UNIV WASHINGTON ;UNIV ST LOUIS (US); ST GEME JOSEPH W III (US); BA) 3 October 1996 (1996-10-03)

D2: GEME J W S ET AL: 'CHARACTERIZATION OF THE GENETIC LOCUS ENCODING HAEMOPHILUS INFLUENZAE TYPE B SURFACE FIBRILS' JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 178, no. 21, November 1996 (1996-11), pages 6281-6287, XP000863110 ISSN: 0021-9193

D3: BARENKAMP S J ET AL: 'IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE HAEMOPHILUS INFLUENZAE' MOLECULAR MICROBIOLOGY,GB,BLACKWELL SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X

Item I

The amendment of Claim 3 is not allowable under Articles 19(2) and 34 (2) (b) PCT. Additional feature "N-truncated protein having the ability to bind to human epithelial cells" is not disclosed in the description as originally filed. For the N-truncated hia proteins it is only described that immunization causes protection against colonization (see Examples).

Item IV

The present set of claims are not linked in manner so as to form a single general inventive concept as required under Rule 13(1) PCT.

The problem underlying the invention of the present application is the provision of a set of nucleotide and amino acid sequences of adhesion (Hia) from non-typeable strains of Haemophilus influenzae.

The solution is represented by the set of amino- and nucleic acid sequences as set forth in SEQ. ID. Nos 23-36.

The international patent application WO9630519 discloses adhesins from non-typeable strains of Haemophilus influenzae, as well as methods for their recombinant production

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA00/00289

and their use in immunogenic compositions and production of antibodies (see abstract, example 3, page 82-84).

Genes from non-typeable H. influenzae coding for Hia adhesins are also disclosed by St. Geme et al. in Infection and Immunity (1998, p. 364-368, see abstract).

Therefore the concept of DNA encoding adhesins from non typeable H. influenzae is not new. In consequence, the different adhesins of the present application fall a posteriori into 6 groups of alleged inventions.

- 1. Claims 1-27 (partially)
 - An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 23 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 24. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 2. SEQ ID NO. 27 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 28. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 3. SEQ ID NO. 29 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 30. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 4. SEQ ID NO. 31 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 32. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.

INTERNATIONAL PRELIMINARY Inte

- 5. An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 33 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 34. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- 6. An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 35 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 36. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.

Item V

1. Novelty:

Claim 3 is not allowable under Article 33 (2) PCT.

Due to the generic and broad definition (especially the wording "truncated" and "expressible" of said claim (see also item VIII) all sorts of H. influenza adhesion encoding nucleotides fall under the definition of Claim 3.

In other words all adhesion nucleotides encoding for any adhesion being shorter (i.e. truncations of only one or two amino acids) than an adhesion of the present application lies within the definition such as those of D1 (see e.g. sequence comparisons of the Search Examiner page 6, in comparison with GSP:R99394 is shorter than no SEQ ID 28).

2. Inventive step

D1 is considered to represent the closest prior art document. D1 teaches Haemophilus adhesion proteins nucleic acids and derived vaccines. SEQ ID NO 36 of the present application has 97% identity with the amino acid sequence of D1, SEQ ID NO 32 has 79% identity with the amino acid sequence of D1 (Sequence Comparisons of the Search Examiner). The problem of the present application is to provide further H. influenza adhesions

INTERNATIONAL PRELIMINARY Inte

International application No. PCT/CA00/00289

proteins and their encoding genes. As soon as one family member of the Haemophilus influenza adhesion protein, its gene the recombinant production and its immunological use is known, it is routine for a skilled person to determine further similar members from other strains of said proteins their immunogenic fragments and their encoding genes.

In this case the cloning and expression, although requiring much work, does not pose such problems so that there was no reasonable expectation of success. For a skilled person it is also obvious to provide non-specified truncated versions of said genes or proteins having no particular unexpected effect (Claim 3).

In consequence, the present claims 1-3, 5-29 are not allowable under Article 33 (3) PCT.

The specific truncated Hia proteins of Claim 4 fulfil the requirements under Article 33(2) and (3) PCT.

The essential difference with D1 is the truncated form wherein the signal sequence is deleted causing a higher expression in E. coli. Said truncated proteins are still immunogenic (see Examples).

The problem of the present application can thus be defined as the provision of alternative hia proteins which can be produced recombinantly in a high amount still causing immunity.

The solution i.e. the truncated hia proteins of claim 4 are not derivable from D1 or any other document cited in the Search Report.

Item VIII

 Claim 2 is formulated in terms of a "product by process". In the PCT contracting states no unified criteria exist concerning this type of claims. Before the EPO such claims, defined in terms of a product by process of manufacture are only admissible if the product as such fulfils the requirements of patentability, i.e. if the products are novel and inventive and if the product cannot be defined by true technical features (Article 6 PCT).

The same applies to claim 15.

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INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

- Independent Claim 3 does not disclose any true technical features. The only 2. characteristic of the claimed nucleic acids is that they are "truncated" and "expressible as inclusion bodies". In consequence, said claim is vague and thus not clear (Article 6 PCT).
- The Applicant should prove whether the strains of Claim 27 are known by the 3. skilled person. Otherwise said claim is not clear.

generate the sites. Upperstrand (SEQ ID No.: 50) lower strand (SEQ ID No.: 51).

Figure 7A shows the construction of plasmids DS-2242-1 and DS-2242-2 that contain the T7 promoter and full-length NTHi strain 33 hia gene, the E. coli cer gene and the kanamycin resistance gene. Restriction enzyme sites are: A, AlwN I; B, BamH I; Bg, Bgl II; H, Hind III; K, Kpn I; N, Nde I; Ps, Pst I; R, EcoR I; S, Sal I; Sm, Sma I; Xb, Xba I; Xho, Xho I. Other abbreviations are: T7p, T7 promoter; ApR, ampicillin resistance; kanamycin KanR, resistance; tt2, trpA; transcription terminator from 1 transcription terminator 2 from T7 gene 10.

Figure 7B shows the oligonucleotides used to generate the 5'-end of the strain 33 his gene coding strand (SEQ ID No.: 52), complementary strand (SEQ ID No.: 53), and encoded amino acid sequence (SEQ ID No.: 54).

Figure 8A shows the construction of plasmid DS-2340-2-3 that contains the T7 promoter and the V38 hia gene from strain 33, the E. coli cer gene and the kanamycin resistance gene. Restriction enzyme sites are: B, BamH I; Bg, Bgl II; H, Hind III; N, Nde I; Ps; PSC I; R, ECOR I; S, Sal I; Sn, SnaB I; Xb, Xba I. T7 promoter; abbreviations are: T7p. Other ampicillin resistance; KanR, kanamycin resistance; ttl, transcription terminator 1 from tt2, transcription terminator 2 from T7 gene 10.

Figure 8B shows the oligonucleotides used to PCR amplify the 5'-end of the truncated his gene. Sense (6286.SL): SEQ ID No: 60, encoded amino acids SEQ ID

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No: 61; antisense (6287.SL) SEQ ID No: 18, complement SEQ ID No: 19, encoded amino acids SEQ ID No: 20.

9A and 9B show the construction Figures plasmids DS-2447-2 and DS-2448-17, that contain tandem copies of the T7 V38 hia (11) and T7 V38 hia (33) genes, respectively. Restriction enzyme sites are: B, BamH I; Bg, Bgl II; H, Hind III; Ps; Pst I; R, EcoR I; S, Sal I; Xb, Xba I. Other abbreviations are: T7p, T7 promoter; ApR, ampicillin resistance; KanR, kanamycin calf alkaline phosphatase; CAP, resistance; trpA; tt2, from terminator transcription transcription terminator 2 from T7 gene 10.

Figure 10 shows the expression of rHia. Panel A: lane 1, full-length rHia (11) no induction; lane 2, full-length rHia (11); lane 3, E21 rHia (11); lane 4, T33 rHia (11); lane 5, V38 rHia (11); lane 6, N52 rHia (11). Panel B: lane 1, V38 rHia (11) no induction; lane 2, V38 rHia (11); lane 3, V38 rHia (11)/cer.

Figure 11 shows a purification scheme for rHia proteins. Abbreviations are: SP, supernatant; PPT, precipitate; DTT, dithiothreitol; OG, octyl glucoside; (x) means discarded.

PAGE analysis of purified rHia. Panel A shows purified V38 rHia protein from strain 11 and panel B shows purified V38 rHia protein from strain 33. Lane 1, molecular weight markers; lane 2, whole-cell lysate; lane 3, crude extract; lane 4, purified rHia protein.

Figure 13, having panels A, B and C, shows the stability of V38 rH1a (11). Panel A shows samples stored at 4°C without glycerol. Panel B shows samples

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Moraxella catarrhalis high molecular weight proteins (200 kDa) from strains 4223 and LES-1 (SEQ ID Nos.: 48, Asterisks within sequences indicate stop codons, indicated sequence they below the but Dots indicate identical residues. The homology. direct . prepared by were alignments seguence the amino acid sequences the comparison οf respective proteins.

Figure 29 shows the oligonucleotides used to PCR amplify the 5' end of the hia gene at the S44 truncated position. Sense (6817.SL) SEQ ID No: 55, encoding amino acids SEQ ID No: 56; antisense (6818.SL) SEQ ID No: 57, complement SEQ ID No: 58, encoded amino acids SEQ ID No: 59.

Figure 30 shows the construction of plasmid JB-2930-3 that contains the S44 hia gene from NTHi strain 11 and the E. coli cer gene and the T7 promoter. Restriction enzyme sites are: B, BamH I; Bg, Bgl II; K, Kpn I; N, Nde I; P, Pst I; R, EcoR I; S, Sal I; Sm, Sma Other Xho, Xho I. Xba I; Xb, Sty I; abbreviations are: T7p, T7 promoter; ApR, ampicillin kanamycin resistance; CAP, resistance; KanR, alkaline phosphatase; ttl transcription terminator 1 from trpA; tt2, transcription terminator 2 from T7 gene 10.

Figure 31 shows SDS-PAGE analysis of the expression of rHia from S44. Lane 1, expression from pET S44 vector at time 0 (no induction); lane 2 expression from pET S44 vector after 4 hours induction; lane 3 expression from JB-2930-3 after 4 hours induction.

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<u>CLAIMS</u>

- 1. An isolated and purified nucleic acid molecule encoding a Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae having:
 - (a) a DNA sequence selected from the group consisting of those shown in Figures 18, 20, 21, 22, 23, 24 and 25 (SEQ ID Nos: 23, 27, 29, 31, 33, 35, 37); or
 - (b) a DNA sequence encoding a Haemophilus influenzae adhesin (Hia) protein having an amino acid sequence selected from the group consisting of those shown in Figures 18, 20, 21, 22, 23, 24 and 25 (SEQ ID Nos: 24, 28, 30, 32, 34, 36, 38).
- 2. An isolated and purified nucleic acid molecule encoding an N-truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus Influenzae which is amplifiable by a pair of nucleotides which are selected from the group consisting of:

SEQ ID No: 7 and SEQ ID No: 15 SEQ ID No: 9 and SEQ ID No: 15 SEQ ID No: 11 and SEQ ID No: 15 SEQ ID No: 13 and SEQ ID No: 15 SEQ ID No: 55 and SEQ ID No: 57

- 3. An isolated and purified nucleic acid encoding an N-truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae expressed as inclusion bodies, said N-truncated protein having the ability to bind to human epithelial cells.
- 4. The nucleic acid molecule of claim 3 which encodes a truncated Hia protein selected from the group consisting of the E21, T33, V38 and N52 truncations of *Haemophilus influenzae* strain 11 and the V38 truncation of *Haemophilus Influenzae* strain 33.
- 5. A vector for transforming a host comprising the nucleic acid molecule of claim 1.
- 6. A vector for transforming a host comprising the nucleic acid molecule of any one of claims 2 to 4.
- 7. The vector of claim 5 or 6 which is a plasmid vector.
- 8. The vector of claim 7 wherein said plasmid vector has the identifying characteristics of a plasmid which is selected from the group consisting of:

SIMBAS→

DS-2008-2-3 as shown in Figure 1A
DS-2186-1-1 as shown in Figure 5A
DS-2201-1 as shown in Figure 5A
DS-2186-2-1 as shown in Figure 5A
DS-2168-2-6 as shown in Figure 5A
IA-191-3-1 as shown in Figure 32

- 9. A vector for transforming a host, comprising a nucleic acid molecule encoding a full-length *Haemophilus Influenzae* adhesin (Hia) protein as claimed in claim 1 or N-truncated *Haemophilus Influenzae* adhesin (Hia) protein as claimed in any one of claims 2 to 4 and a promoter operatively connected to said nucleic acid molecule for expression of said full-length or truncated Hia protein.
- 10. The vector of claim 9 further comprising the cer gene of E. coli.
- 11. The vector of claim 9 which is a plasmid vector.
- 12. The vector of claim 11 wherein said plasmid vector has the identifying characteristics of a plasmid vector which is selected from the group consisting of:

BK-96-2-11 as shown in Figure 6A
DS-2242-1 as shown in Figure 7A
DS-2242-2 as shown in Figure 7A
DS-2340-2-3 as shown in Figure 8A
DS-2447-2 as shown in Figure 9A
DS-2448-17 as shown in Figure 9B
JB-2930-3 as shown in Figure 32

- 13. A host cell transformed by a vector as claimed in claim 5, 6 or 9 and expressing a protective *Haemophilus influenzae* adhesin (Hia) protein of a non-typeable strain of *Haemophilus*.
- 14. The host cell of claim 13 which is a strain of E. coll.
- 15. A recombinant protective Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae producible by the transformed E. coli of claim 14 or an immunogenic fragment thereof.

- An Immunogenic composition, comprising at least one immunologically-active component selected from the group consisting of:
- (A) an isolated and purified nucleic acid molecule encoding a Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae having:
 - (a) a DNA sequence selected from the group consisting of those shown in Figures 18, 20, 21, 22, 23, 24 and 25 (SEQ ID Nos: 23, 27, 29, 31, 33, 35, 37); or

SIMBAS→

- (b) a DNA sequence encoding a Haemophilus influenzae adhesin (Hia) protein having an amino acid sequence selected from the group consisting of those shown in Figures 18, 20, 21, 22, 23, 24 and 25 (SEQ ID Nos: 24, 28, 30, 32, 34, 36, 38);
- (B) an isolated and purified nucleic acid molecule encoding an N-truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae which is amplifiable by a pair of nucleotides which are selected from the group consisting of:

SEQ ID No: 7 and SEQ ID No: 15

SEQ ID No: 9 and SEQ ID No: 15

SEQ ID No: 11 and SEQ ID No: 15

SEQ ID No: 13 and SEQ ID No: 15

SEQ ID No: 55 and SEQ ID No: 57;

- (C) an isolated and purified nucleic acid molecule encoding a truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae expressed as inclusion bodies, said N-truncated protein having the ability to bind to human epithelial cells; and
- (D) a recombinant protective Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae producible by a strain of E. coli transformed by an expression vector as claimed in claim 5, 6 or 9; and

a pharmaceutically-acceptable carrier therefor.

17. The immunogenic composition of claim 18 formulated as a vaccine for in vivo administration to protect against disease caused by Haemophilus.

- 18. The immunogenic composition of claim 16 in combination with a targeting molecule for delivery to specific cells of the immune system or to mucosal surfaces.
- 19. The immunogenic composition of claim 16 formulated as a midroparticle, capsule or liposome preparation.
- 20. The immunogenic composition of claim 16 further comprising an adjuvant.
- 21. A method for inducing protection against disease caused by Haemophilus, comprising administering to a susceptible host an effective amount of the immunogenic composition of claim 16.
- 22. The method of claim 21 wherein the susceptible host is a human.
- 23. A method for the production of a protective Haemophilus influenzae adhesin (Hia) protein of a non-typeable strain of Haemophilus Influenzae, which comprises:

transforming a host with a vector as claimed in claim 6, growing the host cell to express the encoded truncated Hia, and isolating and purifying the expressed Hia protein.

- 24. The method of claim 23 wherein the host cell is E. coli.
- 25. The method of claim 23 wherein said encoded truncated Hia is expressed in inclusion bodies.
- 26. The method of claim 25 wherein said isolation and purification of the expressed Hia is effected by:

disrupting the grown transformed cells to produce a supernatant and the inclusion bodies,

solubilizing the inclusion bodies to produce a solution of the recombinant Hia,

chromatographically purifying the solution of recombinant Hia free from cell debris, and

isolating the purified recombinant Hia protein.

27. The method of claim 23 wherein said non-typeable strain of Haemophilus is selected from the group consisting of strains 11, 33, 32, 29, M4071, K9, K22 and 12.

- 5 -

The method of claim 23 wherein said vector includes the T7 promoter and said E. coli is cultured in the presence of an inducing amount of lactose.

29. A pair of nucleotide sequences capable of amplifying and generating a nucleic acid molecule encoding an N-truncated Haemophilus influenzae adhesin (Hia) protein of a strain of Haemophilus influenzae, which pair of nucleotides is selected from the group consisting of:

SEQ ID No: 7 and SEQ ID No: 15 SEQ ID No: 9 and SEQ ID No: 15 SEQ ID No: 11 and SEQ ID No: 15 SEQ ID No: 13 and SEQ ID No: 15 SEQ ID No: 55 and SEQ ID No: 57

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: RECOMBINANT HAEMOPHILUS INFLUENZAE ADHESIN PROTEINS

(57) Abstract: Recombinant production of Hia protein, in full-length and N-terminally truncated forms, of non-typeable strains of Haemophilus influenzae, is described. The nucleic acid and deduced amino acid sequences of Hia genes of various strains of non-typeable and type c Haemophilus influenzae also are described.



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International application No. PCT/CA 00/00289

	INTERNATIONAL SEARCH REPORT	
	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)	
3ox	Observations where certain claims to the following reasons:	
his	ernational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	
. [Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:	
2.	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:	
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).	
-	II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)	
	International Searching Authority found multiple inventions in this international application, as follows:	
17	International Cost Conf.	
	see additional sheet	
1	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.	
1	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.	t
	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:	t
	of any additional lee.	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 23 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.24 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

2. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 25 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.26 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

3. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.27 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.28 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

4. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.29 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.30 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

5. Claims: 1-27 (in part)

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An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.31 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.32 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compositions containing the same.

6. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.33 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.34 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

7. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.35 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.36 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

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PATENT COOPERATION TREATY

JUL 20 2001

SIM & MEBURNEY BIM. HUBHES, ASHTON & MIKAY

From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

STEWART, Michael I. SIM & McBURNEY 330 University Avenue 6th Floor Toronto, Ontario M5G 1R7 CANADA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

(PCT Rule 71.1)

Date of mailing (day/month/year)

17.07.2001

Applicant's or agent's file reference

1038-1025

international filing date (day/month/year)

international application No. PCT/CA00/00289

16/03/2000

Priority data (day/month/year) 16/03/1999

IMPORTANT NOTIFICATION

Applicant

CONNAUGHT LABORATORIES LIMITED et al

- 1. The applicant is hereby notified that this international Preliminary Examining Authority transmits herewith the International preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and fumish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 69 2399 - 4465

Authorized officer

Neumann, M

Tel.+49 89 2399-7351





7034150813;#24

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

			·		- Name
pplicant's or ag	ents	file reference	FOR FURTHER ACTION	See Notifical	ation of Transmittal of International Examination Report (Form PCT/IPEA/418)
038-1025					Priority date (day/month/year)
itemational app	pilcati	on No.	International filing date (day/mo	onth/year)	16/03/1999
CT/CA00/0	028	9	16/03/2000		18/00/1889
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전 This bee (see	s rep on am e Rui	ort is also accompani	led by ANNEXES, i.e. sheets asis for this report and/or she 607 of the Administrative ins	of the descript	tion, claims and/or drawings which have rectifications made before this Authority the PCT).
3. This rep			elating to the following items:	:	
1	_	Basis of the report			•
ll		Priority	oninion with regard to nove	alty, inventive 8	tep and industrial applicability
111					
įv V	Ø		t under Articio 35(2)-with 189 Nations suporting such staten	ieut to vôaltà! Jeut	Inventive step or industrial applicability;
VI		Certain documents	cited		
VII		Certain defects in th	ne International application	Hon	•
VIII	凶	Certain observation	s on the international applica	X((G))	
Date of sub	miss	on of the demand		Date of complet	ion of this report
11/10/20	00			17.07.2001	
Name and	/ exe!	ng address of the interns	itional .	Authorized offic	per
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INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

International application No. PCT/CA00/00289

			•						
l.	Basis of the report				h have been furnished to				
1.	With regard to the elements of the international application (Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)): Description, pages:								
	1-13,16,17, 19-63	as originally filed							
	14,15,18	as received on	22/06/2001	with letter of	22/06/2001				
	Claims, No.:								
	1-29	as received on	22/06/2001	with letter of	22/06/2001				
	Drawings, sheets:								
	1/83-83/83	as originally filed							
	Sequence listing part of the description, pages:								
	2-75, filed with the letter of 29.05.00								
:	 With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. 								
	These elements were available or furnished to this Authority in the following language: , which is:								
	the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).								
	- and a subjection of the international application (under Rule 48.3(0)).								
	the language of publication of the international appropriate the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).								
	3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:								
	contained in the international application in written form.								
	filed together with the international application in computer readable form.								
	furnished subsequently to this Authority in written form.								
	The state of expensive to this Authority in computer readable form.								
	☑ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure								
	The statement that the information recorded in computer readable form is identical to the written sequence								

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00289

	The	emendments have r	resulted in the cancellation of:				
4.	ine		•				
		the description,	pages:				
		the cialms,	Nos.:	•			
		the drawings,	sheets:				
5.	×		on established as if (some of) the amendments had not been made, sinc eyond the disclosure as filed (Rule 70.2(c)):				
		(Any replacement s	sheet containing such amendments must be referred to under item?	d auuexed to mie			
		see separate shee					
6.	Ad	ditional observations	, if necessary:				
			All are	:			
11	/. La	ack of unity of Inven	ition				
1	, In	response to the Inviti	ation to restrict or pay additional fees the applicant has:				
		restricted the claim	ns.				
	Z	pald additional fee	98.				
] paid additional fee	es under protest.				
			nor paid additional fees.	: The section of the			
	2. C	eg 1 not to invite	and that the requirement of unity of invention is not complied and chose, the applicant to restrict or pay additional fees.				
	3. 1	This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 in					
	1	complied with.					
		osa genarata sh	h for the following reasons: neet				
	4.	 Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report: 					
		🛛 all parts.					
		☐ the parts relating	g to claims Nos				
	V.	Reasoned statemer	nt under Article 35(2) with regard to novelty, inventive step or indu inations supporting such statement	ustrial applicability;			
	4	Statement	•				

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7034150813;#27

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/CA00/00289

Novelty (N)

Yes:

Claims 1-2,4-29

No: Claims 3

Inventive step (IS)

Yes: Claims 4

No:

Yes:

Claims 1-3,5-29

Industrial applicability (IA)

Claims 1-29

No: Claims

2. Citations and explanations see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

INTERNATIONAL PRELIMINARY Inte

International application No. PCT/CA00/00289

D1: WO 96 30519 A (UNIV WASHINGTON ;UNIV ST LOUIS (US); ST GEME JOSEPH W III (US); BA) 3 October 1996 (1996-10-03)

D2: GEME J W S ET AL: 'CHARACTERIZATION OF THE GENETIC LOCUS ENCODING HAEMOPHILUS INFLUENZAE TYPE B SURFACE FIBRILS' JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 178, no. 21, November 1996 (1996-11), pages 6281-6287, XP000863110 ISSN: 0021-9193

D3: BARENKAMP S J ET AL: 'IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE HAEMOPHILUS INFLUENZAE' MOLECULAR MICROBIOLOGY,GB,BLACKWELL SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X

Item I

The amendment of Claim 3 is not allowable under Articles 19(2) and 34 (2) (b) PCT. Additional feature "N-truncated protein having the ability to bind to human epithelial cells" is not disclosed in the description as originally filed. For the N-truncated his proteins it is only described that immunization causes protection against colonization (see Examples).

item IV

The present set of claims are not linked in manner so as to form a single general inventive concept as required under Rule 13(1) PCT.

The problem underlying the invention of the present application is the provision of a set of nucleotide and amino acid sequences of adhesion (Hia) from non-typeable strains of Haemophilus influenzae.

The solution is represented by the set of amino- and nucleic acid sequences as set forth in SEQ. ID. Nos 23-36.

The international patent application WO9630519 discloses adhesins from non-typeable strains of Haemophilus influenzae, as well as methods for their recombinant production

INTERNATIONAL PRELIMINARY International ep EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/CA00/00289

and their use in immunogenic compositions and production of antibodies (see abstract,

Genes from non-typeable H. influenzae coding for Hia adhesins are also disclosed by St. Geme et al. in Infection and Immunity (1998, p. 364-368, see abstract).

Therefore the concept of DNA encoding adhesins from non typeable H. influenzae is not new. In consequence, the different adhesins of the present application fall a posteriori into 6 groups of alleged inventions.

1. Claims 1-27 (partially)

example 3, page 82-84).

- An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 23 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 24. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- 2. An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 27 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 28. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- 3. An isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 29 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 30. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- 4. An Isolated and purified nucleic acid molecule having a sequence as set forth in SEQ ID NO. 31 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 32. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.

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INTERNATIONAL PRELIMINARY

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EXAMINATION REPORT - SEPARATE SHEET

- An isolated and purified nucleic acid molecule having a sequence as set forth in 5. SEQ ID NO. 33 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 34. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.
- An isolated and purified nucleic acid molecule having a sequence as set forth in 6. SEQ ID NO. 35 encoding an polypeptide of a Haemophilus influenzae adhesion having the primary structure as set forth in SEQ ID NO. 36. Vectors for the recombinant production of said adhesion, immunogenic compositions containing the same.

Item V

Novelty: 1.

Claim 3 is not allowable under Article 33 (2) PCT.

Due to the generic and broad definition (especially the wording "truncated" and "expressible" of said claim (see also item VIII) all sorts of H. influenza adhesion encoding nucleotides fall under the definition of Claim 3.

In other words all adhesion nucleotides encoding for any adhesion being shorter (i.e. truncations of only one or two amino acids) than an adhesion of the present application lies within the definition such as those of D1 (see e.g. sequence comparisons of the Search Examiner page 6, in comparison with GSP:R99394 is shorter than no SEQ ID 28).

Inventive step 2.

D1 is considered to represent the closest prior art document. D1 teaches Haemophilus adhesion proteins nucleic acids and derived vaccines. SEQ ID NO. 36 of the present application has 97% identity with the amino acid sequence of D1, SEQ ID NO 32 has 79% Identity with the amino acid sequence of D1 (Sequence Comparisons of the Search Examiner).

The problem of the present application is to provide further H. Influenza adhesions

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INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

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proteins and their encoding genes. As soon as one family member of the Haemophllus influenza adhesion protein, its gene the recombinant production and its immunological use is known, it is routine for a skilled person to determine further similar members from other strains of said proteins their immunogenic fragments and their encoding genes.

In this case the cloning and expression, although requiring much work, does not pose such problems so that there was no reasonable expectation of success. For a skilled person it is also obvious to provide non-specified truncated versions of said genes or proteins having no particular unexpected effect (Claim 3).

In consequence, the present claims 1-3, 5-29 are not allowable under Article 33 (3) PCT.

The specific truncated Hia proteins of Claim 4 fulfil the requirements under Article 33(2) and (3) PCT.

The essential difference with D1 is the truncated form wherein the signal sequence is deleted causing a higher expression in E. coli. Said truncated proteins are still immunogenic (see Examples).

The problem of the present application can thus be defined as the provision of alternative hia proteins which can be produced recombinantly in a high amount still causing immunity.

The solution i.e. the truncated hia proteins of claim 4 are not derivable from D1 or any other document cited in the Search Report.

Item VIII

Claim 2 is formulated in terms of a "product by process". In the PCT contracting states no unified criteria exist concerning this type of claims. Before the EPO such 1. claims, defined in terms of a product by process of manufacture are only admissible if the product as such fulfile the requirements of patentability, i.e. If the products are novel and inventive and if the product cannot be defined by true technical features (Article 6 PCT).

The same applies to claim 15.

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INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA00/00289

Independent Claim 3 does not disclose any true technical features. The only 2. characteristic of the claimed nucleic acids is that they are "truncated" and "expressible as inclusion bodies". In consequence, said claim is vague and thus not clear (Article 6 PCT).

The Applicant should prove whether the strains of Claim 27 are known by the 3. skilled person. Otherwise said claim is not clear.

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PATENT COOPERATION TREATY

INTERNATIONAL SEARCH REPORT

		(PCT Article 18 and Hules 43 and 44)	
Applicant's or agent's	s file reference	FOR FURTHER See Notification of	f Transmittal of international Search Report 20) as well as, where applicable, hem 5 below.
038-1025		ACTION	·
nternational applica	tion No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/CA 00/00289 16/03/2000		16/03/1999	
applicant			
	BORATORIES LI	MITED	
This International saccording to Article	Search Report has bee e 16. A copy is being tr	n prepared by this international Searching Aut ansmitted to the International Bureau.	thority and is transmitted to the applicant
This International	Search Report consists Is also accompanied by	of a total of sheets. a copy of each prior art document cited in this	s report.
1. Basia of the	report		A southerston in the
a. With rega langua ge	rd to the lenguage, the In which it was filed, un	international search was carried out on the bales otherwise indicated under this item.	ssis of the International application in the
□ *	ne international search (urbority (Rule 23.1(b)).	was carried out on the basis of a translation of	the International application furnished to this
b. With rega	ird to any nucleotide a	nd/or amino acid sequence disclosed in the ne sequence listing: ional application in written form.	international application, the international search
	lad together with the in	emational application in computer readable fo	orm.
		to this Authority in written form.	
	umished subsequently	to this Authority in computer readble form.	
X 8	ntemational abblication	ubsequently furnished written sequence listing as filed has been furnished.	
X t	he statement that the in umished	formation recorded in computer readable for	n is identical to the written sequence listing has been
2.	Certain claims were fo	und unsearchable (See Box I).	
	Unity of invention is is		
4. With regard	to the title.		
[X]	the text is approved as	submitted by the applicant.	
		dished by this Authority to read as follows:	· .
	to the abstract,		
		submitted by the applicant. blished, according to Rule 38.2(b), by this Au the date of mailing of this international search	thority as it appears in Box III. The applicant may, In report, submit comments to this Authority.
		ublished with the abstract is Figure No.	
	as suggested by the ap		X None of the figures.
		falled to auggest a figure.	•
		tter characterizes the invention.	

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INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 00/00289

A. CLASSIFICATION OF SUBJECT MATTER
1PC 7 CO7K14/285 C12N15/00 A61K38/00

According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols) IPC 7 CO7K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical search terms used)

STRAND, WPI Data, EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	
X	WO 96 30519 A (UNIV WASHINGTON ; UNIV ST LOUIS (US); ST GEME JOSEPH W III (US); BA)	1-27
	3 October 1996 (1996-10-03) abstract example 3 page 82 -page 84	
X	GEME J W S ET AL: "CHARACTERIZATION OF THE GENETIC LOCUS ENCODING HAEMOPHILUS INFLUENZAE TYPE B SURFACE FIBRILS" JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 178, no. 21, November 1996 (1996-11), pages 6281-6287, XP000863110 ISSN: 0021-9193 tile whole document	1-27

X Further documents are listed in the continuation of box C.	Y Patent tamily members are listed in annex.
*Special categories of ched documents: *A' document defining the general state of the last which is not consider the property of the constant that the manuscript is an explicitly in the control of the	The later document published efter the international filing date of priority date and not in conflict with the application but cled to understand the principle or theory underlying the invention "X" gournment of particular representative internal in considered to cannot be considered nowel or cannot be considered to trivolve an inventive step when the document to taken alone trivolve an inventive step when the document to taken alone ments, such combination being obvious to a person of the first off. "8" decument the trivology particular report "8" decument the trivology particular report Date of mailing of the international search report
13 February 2001	
Name and mailing address of the ISA European Patent Office, P.B. 6818 Patentiaen 2 NL = 2280 HV Ritawik Tel. (+31-70) 340-2040, Tx. \$1 651 epo ni, Fax: (+31-70) 840-3016	Panzica, G

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INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 00/00289

	PCT/CA 00/00289	
DOCUMENTS CONSIDERED TO BE RELEVANT		
Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	
BARENKAMP S J ET AL: "IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE HAFMOPHTIUS INFLUENZAE"	1-27	
SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X the whole document		
ST GEME III J W ET AL: "Prevalence and distribution of the hmw and his genes and the HMW and His adhesins among genetically diverse strains of nontypeable Haemophilus the transport and the transport and the transport and the transport and t	1-27	
FOR MICROBIOLOGY. WASHINGTON, vol. 66, no. 1, January 1998 (1998-01), pages 364-368, XP002137980 the whole document		
WO 96 02648 A (AMERICAN CYANAMID CO; BACTEX INC (US); GREEN BRUCE A (US); BRINTON) 1 February 1996 (1996-02-01) the whole document		
US 5 843 463 A (KRIVAN HOWARD C ET AL) 1 December 1998 (1998-12-01) the whole document		
	BARENKAMP S J ET AL: "IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE HAEMOPHILUS INFLUENZAE" MOLECULAR MICROBIOLOGY, GB, BLACKWELL SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X the whole document ST GEME III J W ET AL: "Prevalence and distribution of the hmw and his genes and the HMW and His adhesins among genetically diverse strains of nontypeable Haemophilus influenzae" INFECTION AND IMMUNITY US AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, vol. 66, no. 1, January 1998 (1998-01), pages 364-368, XP002137980 the whole document WO 96 02648 A (AMERICAN CYANAMID CO; BACTEX INC (US); GREEN BRUCE A (US); BRINTON) 1 February 1996 (1996-02-01) the whole document US 5 843 463 A (KRIVAN HOWARD C ET AL) 1 December 1998 (1998-12-01)	Chatton of document, with indication, where appropriate, of the relevant passages BARENKAMP S J ET AL: "IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE HAEMOPHILUS INFLUENZAE" MOLECULAR MICROBIOLOGY, GB, BLACKWELL SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X the whole document ST GEME III J W ET AL: "Prevalence and distribution of the hmw and hia genes and the HMW and Hia adhesins among genetically diverse strains of nontypeable Haemophilus 1AFIUAPHRAE!" INFECTION AND IMMUNITY, US AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, vol. 66, no. 1, January 1998 (1998-01), pages 364-368, XP002137980 The whole document WO 96 02648 A (AMERICAN CYANAMID CO; BACTEX INC (US); GREEN BRUCE A (US); BRINTON) 1 February 1996 (1996-02-01) the whole document US 5 843 463 A (KRIVAN HOWARD C ET AL) 1-27

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7034150813;#19

International Application No. PCTAA 00 00289

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 23 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.24 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

2. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 25 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.26 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

3. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.27 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.28 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

4. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.29 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.30 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

5. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.31 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.32 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic

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7034150813;#20

International Application No. PCT.CA 00 00289

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

compositions containing the same.

6. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.33 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.34 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

7. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.35 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.36 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

page 2 of 2

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INTERNATIONAL SEARCH REPORT

International application No. PCT/CA 00/00289

	INTERNATIONAL SEATOTT ILL	
Box I	Observations where certain claims were found unsearchable (Contin	ustion of item 1 of first aheet)
	emational Search Report has not been established in respect of certain claims unde	
1.	Claims Nos.: because they relate to subject matter not required to be searched by this Authority	y, namety:
2.	Claims Nos.: because they relate to parts of the international Application that do not comply when they relate to parts of the international Search can be carried out, specifically an extent that no meaningful international Search can be carried out, specifically.	ith the prescribed requirements to such :
з. [Claims Nos.: because they are dependent claims and are not drafted in accordance with the	
Box	II Observations where unity of invention is lacking (Continuation of	ttem 2 of first sheet)
	international Searching Authority found multiple inventions in this international appli	
	see additional sheet	
1. [As all required additional search fees were timely paid by the applicant, this in searchable claims. As all searchable claims could be searched without effort justifying an additional searchable claims.	
3.	of any additional fee. As only some of the required additional search fees were timely paid by the covers only those claims for which fees were paid, specifically claims Nos.:	
4.	No required additional search fees were timely paid by the applicant. Consinestricted to the invention first mentioned in the claims; it is covered by claim	equently, this international Search Report is ms Nos.:
F		tess were accompanied by the applicant's protest.

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INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/CA 00/00289

Patent document cited in search report	Publication date	Patent family member(e)	Publication date
WO 9630519 A	03-10-1996	US 5646259 A AU 718392 B AU 5322896 A CA 2216292 A EP 0815236 A JP 11502713 T	08-07-1997 13-04-2000 16-10-1996 03-10-1996 07-01-1998 09-03-1999
WO 9602648 A	01-02-1996	US 5643725 A US 5834187 A US 5968769 A AU 706937 B AU 3097295 A CA 2195090 A EP 0771352 A	01-07-1997 10-11-1998 19-10-1999 01-07-1999 16-02-1996 01-02-1996 07-05-1997
US 5843463 A	01-12-1998	CA 2138765 A EP 0647139 A JP 2805174 B JP 7509693 T W0 9400149 A US 5721115 A US 5679547 A AT 176989 T CA 2098598 A DE 69130955 D DE 69130955 T DK 565590 T EP 0565590 A ES 2131066 T JP 6508346 T W0 9210936 A	06-01-1994 12-04-1995 30-09-1998 26-10-1995 06-01-1994 24-02-1998 21-10-1997 15-03-1999 22-06-1992 08-04-1999 01-07-1999 27-09-1999 20-10-1993 16-07-1999

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PATENT COOPERATION TREATY

MBAS→

7034150813;#13 **PECFIVED**

FEB 26 2001

SIM & MOBURNLEY SIM, HUBHICO, ASTITON & MAKAY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
SIM & McBURNEY
Attn. Stewart, Michael, I.
330 University Avenue
6th Floor
Toronto, Ontario M5G 1R7
CANADA

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT -OR THE DECLARATION

(PCT Rule 44.1)

CANADA	;
	Date of mailing (day/month/year) 20/02/2001
1038-1025	FOR FURTHER ACTION
International application No. PCT/CA 00/ 00289	International filing date (day/month/year) 16/03/2000
Applicant	
CONNAUGHT LABORATORIES LIMITED	

				the state of the s
1.	X			otified that the international Search Report has been established and is transmitted herewith.
			amendments a icant is entitled, i	nd statement under Article 19: If he so wishes, to amend the cisims of the international Application (see Rule 48):
		When?	The time ilmit for international Se	or filing such amendments is normally 2 months from the date of transmittal of the earth Report; however, for more details, see the notes on the accompanying sheet.
		Where?	Directly to the	International Bureau of WIPO 34, chamin des Colombettes 1211 Geneva 20, Switzerland Fascimile No.: (41-22) 740.14:35
		For mos	re detailed instr	uctions, see the notes on the accompanying sheet.
4	2	The app Article 1	dicant is hereby r 7(2)(a) to that eff	notified that no International Search Report will be cotabilence and रोक्स क्षेट्र नेस्टांबाबां शिल्ला निवास ह leat is transmitted herewith.
:	a	☐ With re	gard to the prot	set against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
		_	_	r with the decision thereon has been transmitted to the international Bureau together with the to forward the texts of both the protest and the decision thereon to the designated Offices.
		no	o decision has be	en made yet on the protest; the applicant will be notified as soon as a decision is made.
		urther action		plicant is reminded of the following:
		If the applic priority clai completion	cant wishes to av m, must reach th of the technical	the priority date, the international application will be published by the international Bureau. old or postpone publication, a notice of withdrawal of the international application, or of the left international Bureau as provided in Rules 80 <i>bis.</i> 1 and 90 <i>bis.</i> 3, respectively, before the preparations for international publication.
		Vithin 19 me	onthé from the p postpone the enti	nority date, a demand for international prefiminary examination must be filed if the applicant by Into the national phase until 30 months from the priority date (in some Offices even later).
	٧	Vithin 20 m	onthe from the p	riority date, the applicant must perform the prescribed acts for entry into the national phase as which have not been elected in the demand or in a later election within 19 months from the elected because they are not bound by Chapter II.
4				

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentiaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo ni, Fax: (+21-70) 340-3016 Authorized officer

Chantal Meyer

; 9-13-01 ; 2:35PM .;

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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the International phase, the claims may also be amended (or further amended) under Article 34 before the international Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires tater. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the international Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the emendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the international Searching Authority (Rule 48.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filled.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required, in all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Latter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the language of the international application is French, the letter must be in French.

SENT BY: SIMBAS

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filled and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- the claim is unchanged;
- (ii) the claim is cancelled;
- (III) the claim is new:
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]: "Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 38 unchanged; new claims 49 to 51 added."
- (Where originally there were 15 claims and after amendment of all claims there are 11): Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims): "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 18 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 18 and 17 added; all other claims unchanged."
- [Where various kinds of amendments are made]: "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 18 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 18 and 17; new claims 20 and 21 added."

"Statement under article 18(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under

The statement will be published with the international application and the amended claims.

it must be in the language in which the international application is to be published.

It must be brief, not exceeding 600 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended, it must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of disations contained in that report. Reference to citations, relevant to a given claim, contained in the international search

report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the international Bureau, also file with the international Bureau, also file with the international Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as flied.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guida.



(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1038-1025	FOR FURTHER see Notification of (Form PCT/ISA/2	of Transmittal of International Search Report 20) as well as, where applicable, item 5 below.
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/CA 00/00289	16/03/2000	16/03/1999
Applicant		
CONNAUGHT LABORATORIES LI	MITED	
This International Search Report has bee according to Article 18. A copy is being tr	en prepared by this International Searching Auth ansmitted to the International Bureau.	nority and is transmitted to the applicant
This International Search Report consists X It is also accompanied by	of a total of sheets. va copy of each prior art document cited in this	report.
Basis of the report		
	international search was carried out on the bas less otherwise indicated under this item.	sis of the international application in the
the international search v Authority (Rule 23.1(b)).	vas carried out on the basis of a translation of th	ne international application furnished to this
was carried out on the basis of th	nd/or amino acid sequence disclosed in the in e sequence listing: onal application in written form.	ternational application, the international search
[ernational application in computer readable form	n
<u> </u>	thic Authority in written form	
	this Authority in computer readble form.	
the statement that the su international application a	bsequently furnished written sequence listing deas filed has been furnished.	oes not go beyond the disclosure in the
the statement that the inf furnished	ormation recorded in computer readable form is	s identical to the written sequence listing has been
	and unsearchable (See Box I).	
3. X Unity of invention is lac	king (see Box II).	
4. With regard to the title,		
$oxed{X}$ the text is approved as su	ubmitted by the applicant.	
the text has been establis	shed by this Authority to read as follows:	
		·
5. With regard to the abstract,		
	ubmitted by the applicant.	
the text has been establis within one month from the	shed, according to Rule 38.2(b), by this Authorit e date of mailing of this international search rep	y as it appears in Box III. The applicant may, ort, submit comments to this Authority.
6. The figure of the drawings to be pub	lished with the abstract is Figure No.	<u> </u>
as suggested by the appl	icant.	X None of the figures.
because the applicant fai	led to suggest a figure.	
because this figure better	characterizes the invention.	

Form PCT/ISA/210 (first sheet) (July 1998)

International Application No PCT/CA 00/00289

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/285 C12N15/00 A61K38/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 $\begin{array}{ll} \text{Minimum documentation searched (classification system followed by classification symbols)} \\ \text{IPC 7} & \text{C07K} \end{array}$

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

STRAND, WPI Data, EPO-Internal, BIOSIS

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 30519 A (UNIV WASHINGTON ;UNIV ST LOUIS (US); ST GEME JOSEPH W III (US); BA) 3 October 1996 (1996-10-03) abstract example 3 page 82 -page 84	1-27
X	GEME J W S ET AL: "CHARACTERIZATION OF THE GENETIC LOCUS ENCODING HAEMOPHILUS INFLUENZAE TYPE B SURFACE FIBRILS" JOURNAL OF BACTERIOLOGY, US, WASHINGTON, DC, vol. 178, no. 21, November 1996 (1996-11), pages 6281-6287, XP000863110 ISSN: 0021-9193 the whole document	1-27

 Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed 	 'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention 'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone 'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. '&' document member of the same patent family
Date of the actual completion of the international search 13 February 2001	Date of mailing of the international search report 2 0. 2. 01
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Panzica, G

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International Application No PCT/CA 00/00289

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT Category Citation of document, with indication, where appropriate, of the relevant passages	
oracion of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
BARENKAMP S J ET AL: "IDENTIFICATION OF A SECOND FAMILY OF HIGH-MOLECULAR-WEIGHT ADHESION PROTEINS EXPRESSED BY NON-TYPABLE HAEMOPHILUS INFLUENZAE" MOLECULAR MICROBIOLOGY,GB,BLACKWELL SCIENTIFIC, OXFORD, vol. 19, no. 6, 1996, pages 1215-1223, XP000579265 ISSN: 0950-382X the whole document	1-27
ST GEME III J W ET AL: "Prevalence and distribution of the hmw and hia genes and the HMW and Hia adhesins among genetically diverse strains of nontypeable Haemophilus influenzae" INFECTION AND IMMUNITY, US, AMERICAN SOCIETY FOR MICROBIOLOGY. WASHINGTON, vol. 66, no. 1, January 1998 (1998-01), pages 364-368, XP002137980 ISSN: 0019-9567 the whole document	1-27
WO 96 02648 A (AMERICAN CYANAMID CO; BACTEX INC (US); GREEN BRUCE A (US); BRINTON) 1 February 1996 (1996-02-01) the whole document	1-27
US 5 843 463 A (KRIVAN HOWARD C ET AL) 1 December 1998 (1998-12-01) the whole document	1-27

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 23 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.24 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

2. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No. 25 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.26 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

3. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.27 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.28 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

4. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.29 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.30 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

5. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.31 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.32 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

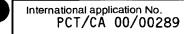
compositions containing the same.

6. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.33 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.34 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.

7. Claims: 1-27 (in part)

An isolated and purified nucleic acid molecule having a sequence as set forth in Seq.Id.No.35 of the sequence listing, encoding for an aminoacid molecule of an Haemophilus influenzae adhesin having primary structure as set forth in Seq.Id.No.36 of the sequence listing. Vectors for the recombinant production of said adhesin, immunogenic compositions containing the same.



Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)	
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:	
1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:	
Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:	
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).	
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)	
This International Searching Authority found multiple inventions in this international application, as follows:	
see additional sheet	
1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.	
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.	
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:	
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:	
Remark on Protest The additional search fees were accompanied by the applicant's protest. X No protest accompanied the payment of additional search fees.	

formation on patent family members

International Application No PCT/CA 00/00289

Patent document		Publication	Patent family Publication		
cited in search report		date	member(s)		date
WO 9630519	A	03-10-1996	US	5646259 A	08-07-1997
MO 3020213	^	00 10 1330	AU	718392 B	13-04-2000
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			US	5968769 A	19-10-1999
			AU	706937 B	01-07-1999
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			DE	69130955 T	01-07-1999
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			EP	0565590 A	20-10-1993
			ES	2131066 T	16-07-1999
			JP	6508346 T	22-09-1994
			WO	9210936 A	09-07-1992